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EXAMINER	
HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,488	ISHII ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/14/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *3-6,9,13 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,8,10-12,14-16 and 18* is/are rejected.

7)☒ Claim(s) *7,8 and 10-12* is/are objected to.

8)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/20/06;2/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-18 are pending in the instant application.

Election/Restrictions

Applicants' election of Group I, claims 1, 2, 7, 8, 10-12, 14-16 and 18, in the reply filed on 5/14/08 is acknowledged. Applicants do not indicate whether the election is with or without traverse, but because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3-6, 9, 13 and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 2, 7, 8, 10-12, 14-16 and 18 are under consideration.

Specification

The disclosure is objected to because of the following informalities:

At page 21, line 15, the term "CA-TRX" is used. This term is not described in the specification, and appears be a typographical mistake for the "(CS)TRX" referred to on line 5 of the same page.

Appropriate correction is required.

Claim Objections

Claims 7, 8 and 10-12 are objected to because of the following informalities:

(1) In each of claims 7, 8, 10 and 11, the parenthetical recitation of "(A represents any amino acid other than Cys)" should be integrated in the claim without parenthesis, for example as "wherein A represents any amino acid other than Cys".

(2) Claim 10 is missing a period following the claim number. Each of the other claims has a period following the claim number (e.g., "1. A human modified thioredoxin...). The claims should be punctuated consistently.

(3) Claim 12 is objected to for reciting …"the above biologically active substance". For clarity, the claim should recite "said biologically active substance" or "the biologically active substance".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 8, 14-16 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, part (c), recites "in positions except for positions 32 and 35, preferably positions 32 to 35 in the amino acid sequence of SEQ ID NO: 2". This recitation is indefinite because it is contradictory. Specifically, it first excludes mutations in positions 32 and 35, but then preferably indicates that the mutations should be in positions 32 to 35. Thus, it is unclear whether this part of the claim encompasses mutations in positions 32 and 35. For purposes of prosecution, the claim has been interpreted broadly to encompass any variant of SEQ ID NO: 2 having one or more mutations and apoptosis-inducing activity.

Furthermore, use of the term "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). That is, it is unclear whether the "preferred" limitation is required by the claim or not.

Claim 1, part (d), refers to "the cysteine residue" in SEQ ID NO: 2, but it is not clear whether this refers to a particular cysteine residue in SEQ ID NO: 2, or encompasses all of the cysteine residues. As shown in Sequence Listing filed on

12/4/06, SEQ ID NO: 2 contains five cysteine residues at positions 32, 35, 62, 69 and 73. The recitation of "the cysteine residue" could refer to any of these positions.

Claim 8 provides for the use of a polypeptide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

See also the rejection of claim 8 below in the section titled "Claim Rejections - 35 USC § 101".

In claim 18, use of the term "if necessary" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). In other words, the claim is indefinite because it is unclear whether or not the claim requires a pharmaceutically acceptable carrier, excipient or diluting agent.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 8 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

See also the rejection of claim 8 above in the section titled "Claim Rejections - 35 USC § 112, second paragraph".

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7, 8, 10-12, 14-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a human modified thioredoxin protein comprising an amino acid sequence of SEQ ID NO: 2 (wild type human thioredoxin) with a substitution at position 32, 35 or both and (2) a complex, agent, enhancer or composition comprising said protein, does not reasonably provide enablement for the human modified thioredoxin protein of claims 1 or 2, the polypeptide of claims 7 or 8, the complex of claims 10-12, the agent of claims 14 and 16, the enhancer of claim 15 or the medicine or pharmaceutical composition of claim 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a genus of variants of human thioredoxin (SEQ ID NO: 2, 105 amino acids), and complexes, agents, enhancers and compositions comprising said protein. The scope of the claims is as follows. Claim 1 encompasses "a human modified thioredoxin" comprising a substitution or modification of the cysteine at residue 35 of SEQ ID NO: 2. The modifications are not limited to the alteration of residue 35, but also include mutations at other residues of SEQ ID NO: 32. Furthermore, part (c) appears to encompass polypeptides with mutations at any other position in SEQ ID NO: 2 and that have "apoptosis-inducing activity". Part (d) encompasses polypeptides with a substitution of any cysteine residue in SEQ ID NO: 2, which contains five cysteine residues at positions 32, 35, 62, 69 and 73, and further

encompasses polypeptides encoded by DNA that can hybridized with said mutants "under a stringent condition"; thus this part of the claim encompasses additional mutations to the sequence. Claim 2 is of similar scope to claim 1 except that substitution of cysteines is limited to serine residues. Claim 7 encompasses any polypeptide comprising Cys-Gly/Pro-Pro/Tyr/His-A, wherein A is any amino acid other than cysteine. No structure is required other than the recited tetrapeptide. Claim 8 is directed to "use" of a polypeptide of the same scope as claim 7. Claim 10 is directed to a "biologically active substance complex" that is "capable of being internalized into cells" and including a biologically active substance bound to a polypeptide of the same scope as claim 7. Claim 11 depends from claim 10 and limits the polypeptide to one that has a substitution at residue 35 of SEQ ID NO: 2. Claim 12 depends from claim 10 and 11 and limits the substance to a "protein or polypeptide". Claims 14 and 15 are directed to an anti-cancer agent or enhancer comprising a modified thioredoxin of claim 1 or 2. Claim 16 is directed to an anti-cancer agent composition comprising a modified thioredoxin of claim 1 or 2 and another anti-cancer agent. Claim 18 is directed to a medicine or a pharmaceutical composition comprising the complex of any of claims 10-12 and optionally a pharmaceutically acceptable carrier, excipient or diluting agent.

The specification provides the following working examples in support of the claimed invention. Example 1 (pg 16-18) describes "[p]roduction of recombinant TRX [thioredoxin] wild type and modified TRX" in an *E. coli* expression system. This examples describes construction of modified thioredoxins with the cysteine residues at positions 32 and/or 35 of SEQ ID NO: 2 replaced with serine residues, including TRX-C32S (SEQ ID NO: 14), TRX-C35S (SEQ ID NO: 12) and TRX-C32S/C35S (SEQ ID NO: 13). Example 2 (pg 18-19) describes "[i]nternalization of recombinant TRX wild type or modified TRX into cultured cell". Part 1 describes the "[b]inding capacity to cells" of fluorescently labeled thioredoxin variants (as analyzed by flow cytometry) and reports that "only the TRX-C35S could be bound to the cells", which were "an HTLV-1 infected human T cell line, ATL2". This part further reports that, "binding was inhibited in the coexistence of the TRX-WT in a largely excessive amount" (pg 19). Part 2 describes incubation of histidine-tagged thioredoxin variants with ATL2 cells followed by Western

blotting of the cytosol fraction of said cells, and reports that "only the TRX-C35S was detected in the cytosol fraction" (pg 19). Example 3 (pg 20) describes the "[b]iological activity of TRX wild type or modified TRX". Part 1 describes "[a]poptosis inducing activity", reporting that apoptosis of human Jurkat T cells "was further facilitated in Jurkat cells with intracellular high expression of the TRX-C35S compared with Jurkat cells to which the TRX-WT or TRX-C32S/C35S had been introduced" (pg 20; Figure 4). Part 2 reports that stimulation of proliferation of cultured human peripheral blood mononuclear cells (as measured by tritiated thymidine incorporation) was increased by TRX-WT and inhibited by TRX-C35S (pg 20; Figure 5). Example 4 (pg 20-22) has two parts, each titled "enhancing the effect of anti-cancer agent behavior". Part 1 describes measurement of apoptosis of Jurkat cells expressing each of the thioredoxin variants following incubation with the anti-cancer drug cisplatin, and reports that cells expressing C35S-TRX had four times as many dead cells as cells expressing the wild type or double mutant TRX. Part 1 describes measurement of apoptosis of Jurkat cells following incubation with C35S-TRX and the anti-cancer drug cisplatin, and reports that that addition of the C35S-TRX increased the number of double-positive cells as compared to a control (no addition) in a time and concentration dependent manner.

Thus, Applicants' results show that a modified thioredoxin of SEQ ID NO: 2 with a serine replacing cysteine at residue 35 can bind to cells and be internalized, but that this functional activity is not present in wild type thioredoxin (SEQ ID NO: 2) or when a second mutation at residue 32 is introduced. Applicants' results further show that a modified thioredoxin of SEQ ID NO: 2 with a serine replacing cysteine at residue 35 can induce apoptosis of a cancerous cell line (Jurkat T cells) to a higher degree than wild type thioredoxin.

As described above, the mutated thioredoxin variants of the claims are not limited to ones in which the cysteine at residue 35 is mutated. Instead, the claims encompass an essentially unlimited number of mutations. Some claims recite functional limitations for the variants such as "having an apoptosis-inducing activity" or "capable of being internalized into cells"; however, other claims contain no such functional limitations and thus encompass both function and non-functional variants.

Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to a protein of SEQ ID NO: 2 with a substitution at position 35 (e.g., C35S-TRX) and variants of said protein. If a variant of the protein is to have a structure and function similar to C35S-TRX, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to C35S-TRX. Conversely, if a protein variant of C35S-TRX need not have a disclosed property then the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Furthermore, the specification itself provides evidence that even one or two amino acid changes (e.g., mutating the cysteine at residue 32 or 35 of SEQ ID NO: 2) can drastically affect the activity of the protein variant.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al*. (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 2, 7, 8, 10-12, 14-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, part (c) is directed to "a polypeptide having an amino acid sequence having one or more substituted, deleted, inserted or added amino acids in positions except for positions 32 and 35, preferably positions 32 to 34 in the amino acid sequence of SEQ ID NO: 2, and having an apoptosis inducing activity". As noted in the section titled "Claim Rejections - 35 USC § 112, 2nd paragraph", this recitation is indefinite because it is contradictory. Specifically, it first excludes mutations in positions 32 and 35, but then preferably indicates that the mutations should be in positions 32 to 35. Thus, it is unclear whether this part of the claim encompasses mutations in positions 32 and 35. However, for purposes of prosecution, the claim has been interpreted broadly to encompass any variant of SEQ ID NO: 2 having one or more mutations and apoptosis-inducing activity. Claims 2 and 14-16 depend from claim 1 and encompass the polypeptide of the same scope or an agent, enhancer or composition comprising a polypeptide of the same scope. However, the specification provides no written description of any variant of SEQ ID NO: 2 that has apoptosis-inducing activity other than mutants with substitutions at residues 32 and/or 35.

Claims 7 and 8 are directed to polypeptides that are "for cell internalization of a biologically active substance", and claims 10-12 and 18 are directed to a complex "capable of being internalized into cells", and compositions thereof. However, the specification provides no written description of any variant of SEQ ID NO: 2 that has apoptosis-inducing activity other than a mutant with a substitution at residue 35. In fact, Example 3 shows that a second mutation at cysteine-32 results in loss of cell binding and internalization.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in

possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides encompassed by the claims; i.e., mutant thioredoxin variants with the recited functional limitations. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed variants as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed” (pg 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of variant polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate

written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only (1) a modified thioredoxin consisting of SEQ ID NO: 2 with a substitution at residue 32 and/or 35 and having apoptosis-inducing activity, and agents comprising said modified thioredoxin, and (2) a polypeptide for cell internalization consisting of SEQ ID NO: 2 with a substitution at residue 35, and complexes comprising said polypeptide, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 7, 8, 10-12, 14-16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al (2002. Circ Res. 90: 1259-1266; published on-line 5/16/02).

Liu teaches "human thioredoxin" (pg 1260, left column) that was used to generate "a single mutant of Trx at the catalytic site C32 or C35 (Trx-C32S or Trx-C35S) and a double-mutant of C32S and C35S (Trx-CS)" (pg 1261, left column).

Claim 1, in part (a), encompasses a "human modified thioredoxin" polypeptide having a substitution of a cysteine at position 35 of SEQ ID NO: 2 with another amino acid. The Sequence Listing filed on 12/4/06 indicates that SEQ ID NO: 2 is a human

sequence and has 105 amino acids, with a cysteine at position 35. Claim 1 does not limit the sequence to a SEQ ID NO: 2 having only a substitution of a cysteine at position 35; instead the claim encompasses any "polypeptide having an amino acid sequence having" said substitution. Therefore, the Trx-C35S sequence and the Trx-CS sequence taught by Liu et al each anticipate claim 1.

Claim 2 depends from claim 1 and limits the "said another amino acid" to serine. As described above, Liu et al teach substitution of serine for the cysteine at position 35 in the Trx-C35S sequence and in the Trx-CS sequence. Therefore, the teachings of Liu et al described above also anticipate claim 2.

The recitation of “for cell internalization of a biologically active substance” in the preamble of claim 7 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. Therefore, independent claim 7 encompasses any polypeptide comprising one of the amino acid sequences recited in the claim such as –Cys-Gly-Pro-A, wherein A is any amino acid other than cysteine. The Trx-C35S sequence taught by Liu et al comprises the sequence Cys-Gly-Pro-Ser (where the Cys is residue 32). This sequence is encompassed by the sequence of "-Cys-Gly-Pro-A" where "A represents any amino acid other than Cys". Therefore, the Trx-C35S sequence taught by Liu et al also anticipates claim 7.

The recitation of “for cell internalization of a biologically active substance” in the concluding statement of claim 8 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. As such, claim 8 encompasses use of any polypeptide comprising one of the recited amino acid sequences. Therefore, claim 8 is anticipated by Liu et al for the same reason as claim 7.

Claim 10 encompasses a "biologically active substance complex capable of being internalized into cells wherein the biologically active substance is bound to a polypeptide comprising an amino acid sequence" represented by –Cys-Gly-Pro-A, where A is any amino acid other than cysteine (such as serine). As described above, the Trx-C35S sequence taught by Liu et al comprises the sequence Cys-Gly-Pro-Ser

(where the Cys is residue 32), and this sequence is encompassed by the sequence of "-Cys-Gly-Pro-A". The term "biologically active" as recited in claim 10 is not defined in the specification and is interpreted broadly to encompass any biologically activity, such as being able to be bound by an antibody. The specification teaches that a "biologically active substance" includes polypeptides (page 14, line 18). The specification further teaches that a "complex" of the invention includes a fusion protein comprising a "biologically active" polypeptide and the modified thioredoxin, and that fusion of a polypeptide with a modified thioredoxin will result in a fusion protein that can be internalized by a cell (page 14, lines 9-10). Liu et al teach Flag-tagged Trx-C35S (see Figure 3 on page 1262), which is a fusion protein comprising the Trx-C35S polypeptide and a Flag epitope tag (which is biologically active in being recognized by an anti-Flag antibody). Such a fusion protein would inherently be "capable of being internalized into cells" because the Trx-C35S portion would provide this functionality. As such, the Flag-tagged Trx-C35S fusion protein taught by Liu et al anticipates claim 10.

Claim 11 depends from claim 10 and limits the polypeptide comprising the –Cys-Gly-Pro-A sequence to one that has a substitution of the cysteine at residue 35 of the human thioredoxin sequence of SEQ ID NO: 2. As described above for claim 10, the Tri-C35S taught by Liu et al has a serine substitution at the cysteine at residue 35 of human thioredoxin (SEQ ID NO: 2). Therefore, the teachings of Liu et al described above anticipate claim 11 for the same reasons as claim 10.

Claim 12 depends from claim 10 and limits the "biologically active substance" to a "protein or polypeptide". As described above for claim 10, Liu et al teach a Flag-tagged Trx-C35S fusion protein and the Flag-tagged portion of this protein is a polypeptide that is a "biologically active substance". Therefore, the teachings of Liu et al described above anticipate claim 12 for the same reasons as claim 10.

The recitation of “anti-cancer” in the preamble of claim 14 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. Therefore, claim 14 encompasses any "agent" composed of the modified thioredoxin of claim 1 or 2. Furthermore, the instant specification defines "modified thioredoxin of the invention" (which include those with a C35S substitution) as

an "anti-cancer" agent. The agent of claim 14 does not require a component other than modified thioredoxin. Therefore, the modified thioredoxins taught by Liu et al (described above for claim 1) also meet the limitations of the "anti-cancer agent" of claim 14.

The recitation of “anti-cancer” in the preamble of claim 15 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. Therefore, claim 14 encompasses any "enhancer" composed of the modified thioredoxin of claim 1 or 2. Furthermore, the instant specification defines "modified thioredoxin of the invention" (which include those with a C35S substitution) as an "anti-cancer enhancer". The enhancer of claim 15 does not require any components other than the modified thioredoxin. Therefore, the modified thioredoxins taught by Liu et al (described above for claim 1) also meet the limitations of the "anti-cancer enhancer" of claim 15.

The recitation of “anti-cancer” in the preamble of claim 16 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. Furthermore, the instant specification defines "modified thioredoxin of the invention" (which include those with a C35S substitution) as an "anti-cancer" agent. Therefore, claim 16 encompasses any "agent composition" comprising the modified thioredoxin of claim 1 or 2 and "another anti-cancer agent". Liu et al describe a composition comprising Trx-C35S bound to the protein ASK1 (pg 1261, left column, "ASK1 bound to Trx-WT, Trx-C32S and Trx-C35S…"). The protein ASK1 is inherently an anti-cancer agent, as evidenced by Chen et al (1999. Oncogene. 18: 173-180; cited here solely to support inherency) who teaches that "overexpression of wild-type ASK1 itself resulted in apoptosis in several cancer lines" (pg 177). Therefore, the composition comprising Trx-C35S bound to ASK1 taught by Liu et al meets the limitations of the "anti-cancer agent composition" of claim 16.

Claim 18 encompasses a "pharmaceutical composition" comprising the complex of any of claims 10-12 "and if necessary a pharmaceutically acceptable carrier, excipient or diluting". The recitation of "if necessary" has been broadly interpreted as an optional limitation. Furthermore, the recitation of "pharmaceutical" in the preamble of claim 18 is interpreted as an intended use and bears no accorded patentable weight to

distinguish a claimed product over one from the prior art. Therefore, claim 18 encompasses a composition comprising the complex of any of claims 10-12. As described above, the Flag-tagged Trx-C35S fusion protein taught by Liu et al meets the limitations of the complex of claim 10. Liu et al further teach cell lysates from endothelial cells expressing the Trx-C35S. This cell lysate is a composition comprising the Trx-C35S. Therefore, the teachings of Liu et al also anticipate claim 18.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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